

Application 10/620,155
June 5, 2007 Reply to Office Action dated May 11, 2007

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REMARKS/ARGUMENTS

I. Status of the claims

Upon entry of the present amendment claims 1 through 22 are pending.

Claim 5 has been amended to more clearly point out and define the claimed invention.

Support for the amendment to claim 5 can be found in the Specification on page 26, lines 4 – 10.

Claim 15 was amended to make the terminology consistent with that used in claim 1 from which it depends.

Claims 23 -24 have been cancelled. Cancellation of subject matter is without prejudice to subsequent revival for prosecution in a divisional or continuation application.

Claims 25 – 34 have been withdrawn from consideration.

The amendments are fully supported by the application as filed and do not introduce new matter. Entry of these amendments is respectfully requested.

II. Election/Restriction

In response to the restriction requirement, Applicants elect with traverse, Group I, claims 1-21 drawn to a low dead volume extraction column.

According to section 803 of the MPEP, where claims can be examined together without undue burden, the Examiner must examine the claims on merits even though they are directed to distinct inventions. In establishing that an "undue burden" would exist for co-examination of claims, the Examiner must show that examination of the claims would involve substantially different prior art searches, making the co-examination burdensome. Here, a proper search of the subject matter of Group I column claims would logically identify prior art relating to Group II claims.

III. Claim rejections under 35 U.S.C. § 112

Claims 23 and 24 were rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention. Claims 23 and 24 have been cancelled obviating the rejection.

IV. Claim rejections under 35 U.S.C. § 103(a)

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Before addressing the individual § 103(a) rejections, Applicants would like to review some definitions and attributes of the low dead volume extraction columns of the instant invention.

The extraction columns of the instant invention out-perform other columns in the areas of analyte purity and yield. Thin, low pore volume frits are essential to the extraction column function. The low pore volume of the frits contributes to the low dead volume of the column. The low dead volume of the column facilitates the elution of the captured analyte in a very small volume of desorption solution, allowing for the preparation of small volume samples containing high concentrations of analyte.

A skilled artisan knows that column dead volume is defined as the interstitial volume present in the extraction bed and frits. The interstitial volume of the bed refers to the volume of the bed of extraction media that is accessible to solvent. In particular, Applicants would like to distinguish between pore thickness, pore volume and porosity. Applicants claim an extraction column having low pore volume frits that are less than 350 microns thick. Pore volume is defined as the volume of liquid required to replace (flush out) liquid in the frit. Pore volume is calculated by multiplying frit thickness by frit area and frit porosity. Frit porosity is a measure of the void spaces in the frit, and is measured as a fraction, between 0–1, or as a percent between 0 – 100%.

A. Stefkovich in view of Dorval et al.

In section 10 on page 5 of the Office action, the Examiner rejected claims 1, 2, 6, 9, 10, 14, 15, and 22-24 as allegedly obvious over Stefkovich et al. (“Stefkovich”, US 5368729) in view of Dorval et al. (“Dorval”, US 5547833). Applicants respectfully traverse the rejection on the grounds that the Examiner has not made a *prima facie* case of obviousness. The MPEP § 2143 states “To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations.”

Applicants assert that the first criterion has not been met. Section 2143.01 (III) of the MPEP states “The mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination. In re Mills, 916 F.2d 680, 16 USPQ2d 1430 (Fed. Cir. 1990)”. Applicants’ careful reading of Stefkovich and

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Dorval revealed no suggestion to combine the extraction device of Stefkovich with elements of Dorval's radial flow assay.

According to section 2144 of the MPEP, The rationale to modify or combine the prior art does not have to be expressly stated in the prior art (Ex parte Clapp, 227 USPQ 972 (Bd. Pat. App. & Inter. 1985)), however the examiner must present a convincing line of reasoning supporting the rejection (Ex parte Levengood, 28 USPQ2d 1300). On page 6 of the Office action, the Examiner alleges "It would have been obvious to a person of ordinary skill in the art to modify Stefkovich by incorporating Dorval's filter, which has a thickness of about 50 microns, to enhance the selectivity of components to be filtered through the column." Applicants respectfully disagree. Applicants argue that the motivation to enhance selectivity of the components to be filtered is not a convincing line of reasoning because filtering is an undesirable function for the frits of the instant invention.

A frit that acts as a filter is undesirable because 1) the filtering action can prevent the analyte from reaching the bed of extraction medium and 2) the frit could become plugged, preventing or limiting the flow of sample components through the bed. The desired characteristics of frit pores are described in Applicants' specification as follows: "The performance of the column is typically enhanced by the use of frits having pore or mesh openings sufficiently large so as to minimize the resistance to flow. The use of membrane screens as described herein typically provide this low resistance to flow and hence better flow rates, reduced back pressure and minimal distortion of the bed of extraction media. The pore or mesh openings of course should not be so large that they are unable to adequately contain the extraction media in the chamber. (page 26, lines 13 – 19)." The fact that Applicants' specification teaches pore sufficiently large so as to minimize the resistance to flow establishes that selective filtering is not a desirable characteristic for the frits. Applicants are using a thin frit to keep the frit pore volume low, however it is still necessary to have sufficient porosity and sufficiently large pores in order minimize flow resistance.

To further illustrate this point, consider for example, the purification of a protein from a cell lysate using the extraction columns of the instant invention. A cell lysate contains particulates such as cell debris so prior to loading the sample on the column the cell lysate is usually centrifuged. Even after centrifugation, some particulate matter can remain in the sample. If the frit functions as a selective filter (e.g. the filter pores are smaller than particulates in the sample), the column will plug, flow will cease and purification of the analyte will not be possible.

In addition, Applicants respectfully submit that the references cited by the Examiner are not sufficient to establish a *prima facie* case of obviousness against the above-cited claims because the

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third criterion for obviousness has not been met. The combination of Stefkovich and Dorval does not teach or suggest each and every limitation of the claims. In particular Stefkovich and Dorval not teach low pore volume frits and frits that can be membrane screens. Applicants' claim 1 teaches a low dead volume extraction column wherein the top frit and the bottom frit have a low pore volume. In section 10 on page 5 of the Office action, the Examiner alleges that the frits of the extraction column taught by Stefkovich have a low pore volume. This is not the case. Stefkovich teaches a solid phase extraction device having sorbent material entrapped between two frits (column 1, lines 8 - 9), however Stefkovich gives no information whatsoever regarding the frit pore volume because Stefkovich does not provide any information regarding frit diameter, porosity or thickness.

Claim 9 is drawn to the low dead volume extraction column of claim 1 wherein the bottom frit is a membrane screen and the top frit is optionally a membrane screen. Stefkovich does not teach each and every element of claim 9. On page 5, the Examiner further states that the top and bottom frits employed by Stefkovich are membrane screens. Again, Applicants argue that this is not the case. Referring to FIG. 1 of Stefkovich, there is an assembly consisting of membrane support 24 having grid 25 and membrane filter 22 directly above upstream frit 26. The membrane filter functions to prevent air from passing through the membrane during operation so the sorbent remains uniformly wet (column 4, lines 41 - 51). So although the device taught by Stefkovich contains a membrane filter proximal to the upstream frit, it is a separate component having a different function. In addition, there is no corresponding membrane filter proximal to the downstream frit.

Dorval does nothing to remedy the deficiencies of Stefkovich. Dorval teaches methods, devices and kits for detection of analytes in very small samples. Dorval's device is not an extraction column for purifying an analyte. Dorval teaches a device for performing test assay comprised of a delivering member for delivering a sample to a test assay surface. "The delivery member includes a prefilter having a sample receiving surface. The prefilter also includes a sample delivering surface for delivering the sample to the test assay surface. A diffusing material is provided on the prefilter sample receiving surface for rapidly and laterally dispersing the sample when applied to the delivering member" (column 2, lines 44-50). In some embodiments, the prefilter is a membrane having a pore size of from about 0.1 micron to 1.0 microns and a thickness of from about 50 microns to about 300 microns (column 3, lines 1-3).

The Examiner alleges "It would have been obvious to a person of ordinary skill in the art to modify Stefkovich by incorporating Dorval's filter, which has a thickness of about 50 micron". However, the filter of Dorval could not be combined with the extraction device taught by Stefkovich

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to achieve the properties of the instant invention. First, although Dorval's membrane has a thickness of less than 350 micron, it would not be suitable for use with the extraction columns of the instant invention because of the pore size. Dorval's membrane is a prefilter having a pore size of from about 0.1 micron to 1.0 microns and a thickness of from about 50 microns to about 300 microns (column 3, lines 1-3). Referring to Applicants' Specification pore size should be in the range of 5 – 100 μm and preferably in the range of 15 – 50 μm (page 31, line 14 – 16) for the frits and columns of the instant invention to achieve the desired performance. Further, Applicants' Specification teaches away from frits having a very small pore size. One page 26, lines 13 – 15, the Specification states "The performance of the column is typically enhanced by the use of frits having pore or mesh openings sufficiently large so as to minimize the resistance to flow." Applicants remind the Examiner that teaching away is indicative of non-obviousness.

Second, the substitution of Dorval's prefilter for the frit taught by Stefkovich is not a simple substitution. Dorval's pre-filter performs a considerably different function than the frits of the instant invention. In Dorval's radial flow assay liquid travels across the pre-filter by diffusion. Diffusion is the spontaneous movement of molecules or other particles in solution, owing to their random thermal motion, to reach a uniform concentration throughout the solvent, a process requiring no addition of energy to the system. A pre-filter that is appropriate for diffusion may have different properties than a frit and is not necessarily suitable for use as a frit. Thus there is no reason to believe that the membrane of Dorval could somehow be inserted into the extraction device taught by Stefkovich and function as a frit. The function of the frits used in the extraction column of the instant invention is to retain the resin bed inside the column of allow liquids to flow through the column. It is not clear Dorval's membrane would retain the medium. And given the very small pore size of Dorval's membrane, it certainly would not have the desired flow characteristics.

Third, Dorval's device performs a radial flow assay which identifies immobilized species. In contrast, the purpose of the extraction columns of the instant invention is analyte purification. It is not clear why a person of ordinary skill in the art of solid phase extraction would even be familiar with the teachings of Dorval.

In summary, there is no suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Further, neither Stefkovich nor Dorval, alone or in combination teach all the elements of claim 1 and claim 9. Therefore, claims 1 and 9 are non-obvious. According to section 2143.03 of the MPEP, "If an independent claim is nonobvious under 35 U.S.C. 103, then any claim

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depending therefrom is nonobvious"¹. Accordingly, since claims 2, 6, 9, 10, 14, 15 and 22 depend from claim 1, they are not obvious. Claims 23 - 24 were cancelled rendering the rejection moot. As no *prima facie* case of obviousness over Stefkovich in view of Dorval has been established, withdrawal of the § 103 rejection is respectfully requested.

B. Ngo et al. and Dorval et al.

In section 11 on page 6 of the Office action, the Examiner rejected claims 1-3, 6-13, 16, 18, 19 and 20 - 24 as allegedly unpatentable over Ngo et al. ("Ngo", US 5219529) and Dorval. Again, Applicants respectfully traverse the rejection on the grounds that the Examiner has failed to establish a *prima facie* case of obviousness.

With regard to the first criterion for establishment of a *prima facie* case of obviousness, Applicants' reading of Dorval and Ngo revealed no suggestion to combine Ngo's cartridge assembly with elements of Dorval's radial flow assay. The examiner provides the following motivation to combine the references. "It would have been obvious to a person of ordinary skill in the art to modify Ngo by incorporating Dorval's filter, which has a thickness of about 50 microns, to enhance the selectivity of components to be filtered through the column." Applicants argued the preceding rejection (Stefkovich in view of Dorval) on the basis that (1) the Examiners alleged motivation to combine the filter used by Dorval with the column of Stefkovich was not a convincing line of reasoning and (2) the particular filter used by Dorval would not be suitable for use in the columns of the instant invention. The very same arguments apply to the combination of Dorval's filter and Ngo's cartridge. Thus, claim 1 is not obvious.

In addition to the lack of motivation to combine the membrane of Dorval with the cartridge of Ngo, there is no reason to believe that the membrane of Dorval could somehow be inserted into Ngo's cartridge and function as a frit. If Dorval's membrane could successfully be integrated into Ngo's cartridge, it is not clear Dorval's membrane would retain the medium. And as explained above, Dorval's membrane would not have the desired flow characteristics.

With regard to the third criterion for establishing a *prima facie* case of obviousness, Applicants respectfully submit that the references cited by the Examiner are not sufficient to establish a *prima facie* case of obviousness against the above-cited claims because neither Ngo nor Dorval, alone or in combination, teach or suggest each and every element of the claims. In particular Ngo does

¹ *In re Fine*, 837 F.2d 1071, 5 USPQ 2d 1596 (Fed. Cir. 1988).

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not teach low pore volume frits, extraction columns having a bed volume of less than 20 μ l, a column body that can be a syringe and frits that can be membrane screens.

Applicants' claim 1 teaches a low dead volume extraction column wherein the top frit and the bottom frit have a low pore volume. In section 11 on page 6 of the Office action, the Examiner states that the frits of the extraction column taught by Ngo have a low pore volume. This is not necessarily the case. Ngo provides ranges of pore sizes and filter thicknesses between 0.5 mm and 6 mm (column 4, lines 5 through 21) however, Ngo does not give enough information to calculate pore volume using the formula given above.

With regard to claim 8, the Examiner states "that the extraction media has a bed volume of less than 20 microliters" and cites column 2, lines 61-69 of Ngo. Referring to column 2, lines 64 and 65, Ngo states "As shown in FIG. 2, cartridge 12, which may, for example have a volume of 0.5 ml, 1 ml or 5 ml" (emphasis added). Thus Ngo's bed volume is at least 500 microliters which is outside the range given in claim 8 of less than 20 microliters. Thus, claim 8 is non-obvious.

Regarding claim 19, the Examiner asserts that the column body taught by Ngo can comprise a syringe (page 7 of the Office action). The Examiner refers to FIG. 1. The syringe in FIG. 1 is attached to Ngo's cartridge but it is a separate component (see column 2, lines 58-60). Consequently, the cartridge taught by Ngo does not comprise a syringe. Thus claim 19 is non-obvious.

With reference to claim 9, the Examiner states the top and bottom frits used by Ngo can be membrane screens. The Examiner cites column 3, line 55 through column 4, line 29. Although Ngo describes various filter materials, pore sizes and thicknesses, Ngo does not specifically teach filters that are membrane screens. Thus claim 9 is non-obvious.

With regard to claim 21, the Examiner maintains "It would have been obvious to a person of ordinary skill in the art to modify Ngo by having Dorval's peristaltic pump because it would be desirable to create a faster and more convenient method of passing fluid through the syringe and column." Yet, the peristaltic pump is not a part of Dorval's invention. Dorval uses the peristaltic pump in Example 3 to run an HPLC column for purifying HIV to be used with their test assay surface (column 23, lines 50 - 53). Thus, claim 21 is non-obvious.

For the reasons stated above, claims 1, 8, 9, 19 and 21 are non-obvious. Further, since claims 1, 8, 9, 19 and 21 depend from claim 1, they are non-obvious. Additionally, since claims 2, 3, 6, 7, 10-13, 16, 18, 20 and 22 depend from claim 1, they are not obvious (MPEP section 2143.03). Claims 22 - 24 were cancelled, obviating the rejection. Since no *prima facie* case of obviousness over Ngo and Dorval has been established, withdrawal of the § 103 rejection is respectfully requested.

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C. Ngo et al. and Dorval et al. in view of Ichikawa et al.

In section 12 on page 8 of the Office action, the Examiner rejected claims 4 and 5 as allegedly unpatentable over Ngo and Dorval in further view of Ichikawa et al. ("Ichikawa", US 4708800). Applicants respectfully traverse the rejection on the grounds that the Examiner has failed to make a *prima facie* case of obviousness.

First, as Applicants argued above, claim 1 is non-obvious over Ngo and Dorval because two of the three basic requirements for establishing a *prima facie* case of obviousness have not been met. The addition of Ichikawa does not render claim 1 obvious. Since claims 4 and 5 depend from claim 1, they are non-obvious (MPEP section 2143.03).

Second, Applicants respectfully submit that with regard to claims 4 and 5, the Examiner has not provided a convincing line of reasoning to combine Ngo, Dorval, and Ichikawa. Further, Ngo, Dorval, and Ichikawa alone or in combination, fail to teach or suggest each and every element of claims 4 and 5. Claim 4 is drawn to a low dead volume extraction column wherein the pore volume is less than or equal to 10% of the interstitial volume and amended claim 5 is drawn to a column in which the bottom frit has a pore volume of 1 ul or less. On page 8 of the Office action, the Examiner states "Ichikawa discloses a porous hollow fiber membrane comprising filters, which have a porosity in the range of 5 to 60%. It would have been obvious to a person of ordinary skill in the art to modify Ngo in view of Dorval by having filters with a pore volume of 0.5 microliters or less (or 10% or less) because it would be convenient to have a filter that ensures a specific amount of fluid passes through the filter at one moment."

In response to the Examiner's assertion, Applicants would like to remind the Examiner of the distinction between pore volume, porosity and interstitial volume. An artisan skilled in chromatography column design knows that pore volume is defined as the volume of liquid required to replace (flush out) liquid in the frit. In contrast, porosity is a measure of the void spaces in the frit, and is a fraction, between 0-1, or as a percent between 0 - 100%. Interstitial volume is described as follows in Applicants' Specification, page 9, lines 8 - 13: "The term "interstitial volume" of the bed refers to the volume of the bed of extraction media that is accessible to solvent, e.g., aqueous sample solutions, wash solutions and desorption solvents. For example, in the case where the extraction media is a chromatography bead (e.g., agarose or sepharose), the interstitial volume of the bed constitutes the solvent accessible volume between the beads, as well as any solvent accessible internal regions of the bead, e.g., solvent accessible pores." With respect to the units associated with each term,

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pore volume and interstitial volume are expressed as a liquid volume (e.g. microliters), while porosity is expressed either as a percent or as a unit-less number between 0 and 1.

Ichikawa discloses a membrane having a porosity in the range of 5 – 60%. Based on the above definitions it is clear claim 4 cannot be held obvious over Ngo and Dorval in further view of Ichikawa. In claim 4 the pore volume is expressed in terms of the interstitial volume which is a liquid volume measurement. Pore volume cannot be equivalent to porosity which is measured as a percentage. Similarly, claim 5 cannot be held obvious over Ngo and Dorval in further view of Ichikawa because pore volume is significantly different from porosity. Therefore, claims 4 and 5 are non-obvious.

Since no *prima facie* case of obviousness over Ngo and Dorval in further view of Ichikawa has been established, withdrawal of the § 103 rejection is respectfully requested.

D. Ngo et al. and Dorval et al. in further view of Becker et al.

In section 13 on page 8 of the Office action, the Examiner rejected claim 17 as allegedly unpatentable over Ngo and Dorval in further view of Becker et al. ("Becker", US 4308204). Again, Applicants respectfully traverse the rejection on the grounds that the Examiner has not made a *prima facie* case of obviousness.

Becker teaches a process for preparing the third component of the complement from human blood plasma (C3). Becker provides an example of C3 purification using a glass column filled with activated agarose having an affinity for C3. For the column preparation, Becker uses 8 grams of agarose.

First, as Applicants argued above, claim 1 is non-obvious over Ngo and Dorval in further view of Becker because two of the three basic requirements for establishing a *prima facie* case of obviousness have not been met. The addition of Becker does not render claim 1 obvious. Since claim 17 depends from claim 1, it is non-obvious (MPEP section 2143.03).

Claim 17 is drawn to a low dead volume extraction column wherein the bed of extraction medium has a dry weight of less than 10 mg. Applicants respectfully propose that the Examiner has not provided a convincing line of reasoning to combine Ngo, Dorval, and Becker. On page 9 of the Office action, the Examiner states "It would have been obvious to a person of ordinary skill in the art to modify Ngo in view of Dorval by having agarose, which has a dry weight of less than 10 mgs, to ensure that a sufficient amount of extraction media is present in the column to isolate or purify the analyte of interest." While claim 17 recites a dry weight of less than 10 mg, Becker uses a dry

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weight of 8 grams. Applicants fail to understand the Examiner's logic with respect to a motivation to combine Becker with Ngo & Dorval.

Lastly, it is clear that the combination of Ngo, Dorval, and Becker fail to teach or suggest each and every element of claim 17. Becker employs a bed of extraction medium having a dry weight of 8 grams which is clearly outside the range of the extraction medium dry weight used in the column disclosed in claim 17 (10 mg). Therefore, claim 17 is non-obvious.

Since no *prima facie* case of obviousness over Ngo and Dorval in further view of Becker has been established, withdrawal of the § 103 rejection is respectfully requested.

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CONCLUSION

Applicants believe no fee is required for submission of this response, however, if a fee is required, the Commissioner is authorized to deduct such fee from the undersigned's Deposit Account No. 50-2852.

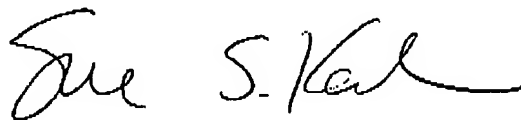
In view of the foregoing, Applicants believe all claims now pending in this application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If a telephone conference would expedite prosecution of this application, the Examiner is invited to telephone the undersigned at (408)267-7214.

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Respectfully submitted,



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